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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,770	11/09/2001	Gary E. Ward	V00139.70050	9181

7590 11/18/2003

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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,770	WARD ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,14,15,17,20,23-26,30,31,34,35,38 and 39* is/are pending in the application.

4a) Of the above claim(s) *3-7,9,17,20,30,31,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14,15,23-26,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.

4) ☐ Interview Summary (PTO-413) Paper No(s). _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: .

DETAILED ACTION

1. Applicant's response filed on 9/4/03 to Office action on restriction is acknowledged. Claims 1-7, 9, 14-15, 17, 20, 23-26, 30, 31, 34-35 and 38-39 are pending in the application.

Priority

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application 60/247,870 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-2, 14-15, 23-26, 38 and 39 drawn to an isolated polypeptide, SEQ.ID.NO: 1 of this application. Therefore, the priority is accorded as of the filing date of the current application 11/9/01.

Drawings

3. No drawings have been filed in the application.

Information Disclosure Statement

4. The Information Disclosure Statement submitted 2/25/02, paper # 3 has been signed and a signed copy of the same is attached here with the office action.

Specification - Informalities

5. Applicant should follow the direction or order or arrangement in framing the specification as provided in 37 CFR 1.77(b) since this is a utility application filed in USA. The specification should include all the sections in order. For example: Claims should begin with "I claim" or "'we claim" or "What is claimed is". Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Election

6. Applicant's election of Group II, Claims 1-2, 14-15, 23-26, 38 and 39 in Paper No. 13 drawn to an isolated Toxoplasma apical membrane antigen (Tg AMA-1), a vaccine comprising said protein is acknowledged.

7. Claims 3-7, 9, 17, 20, 30, 31 and 34-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Since no arguments put forth to support traversel, the requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 14-15, and 38-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a ***Written description rejection.***

Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

Claims are directed an isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1, fusion protein comprising said fragments, vaccine composition comprising said fragment or functionally active variant, said vaccine is a proteosome vaccine for T.gondii.

The instant specification teaches nucleic acid TgAMA1 sequence, SEQ ID NO: 2 and the polypeptide SEQ ID NO: 2, encoded by said nucleic acid from *Toxoplasma gondii.* The specification also teaches that this protein is similar to P.falciparum apical membrane protein (AMA) and involves in parasite invasion into the cell. However, there is no disclosure of antigenic fragment of SEQ.ID.NO: 1, fusion protein comprising said fragments, vaccine composition comprising said fragment or functionally active variant, said vaccine is a proteosome vaccine for T.gondii. Further, the instant specification teaches no potential vaccine composition comprising said TgAMA1 polypeptide or its antigenic fragments or functionally active variant, No specific fragments were described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While, one of skill in the art, may be able to experiment on a wide range of fragments in order to determine which fragment can inhibit the infection, without sufficient description as to where to begin with or which fragment would be an effective vaccine, the specification does not describe by any identifying characteristics or properties of fragments of T.gondii parasite protein. Therefore, the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. These fragments do not meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The

invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The actual structure or other relevant identifying characteristics of each fragment having the claimed properties of the polypeptide, SEQ.ID.NO: 1 can only be determined empirically by actually making every amino acid which can result in fragments which can identity the full length protein.

There must be some nexus between the structure of the polypeptide fragments and the function of that fragment. The specification fails to teach the structure or relevant identifying characteristics of fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. With the exception of an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 1, fragments, fusion protein having said fragments or vaccine composition comprising said are not adequately described. Written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad

10. The rejection of claims 1-2, 14-15 and 38-39 are rejected under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence SEQ.ID.NO: 1, the specification does not reasonably provide enablement for any isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1, fusion protein comprising said fragments, vaccine composition comprising said

fragment or functionally active variant, said vaccine is a proteosome vaccine for *T.gondii.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is maintained as set forth in the previous office action.

The specification describes the polypeptide SEQ ID NO: 1 that is encoded by a polynucleotide sequence, SEQ.ID.NO: 2 from *T.gondii.* The specification fails to indicate the biological activity of said fragments of SEQ ID NO: 1, fails to teach that SEQ ID NO: 1, a polypeptide that is detected by immune or convalescent sera and further lacks any description of polypeptide SEQ ID NO: 1 which acts as a vaccine. The specification is not enabled for fragments because 1) the specification fails to teach that the alleged polypeptide fragments of SEQ ID NO: 1 is able to function as a vaccine composition 2) the specification fails to teach how to make and use fragments thereof that have an unknown and uncharacterized function; 3) the specification fails to teach what are the critical residues that can be modified and still achieve a fragment with any functional activity or any fragments with vaccine characteristics for *T.gondii.* ; 4) the art teaches that polypeptides with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of the polypeptide of SEQ ID NO: 1 as a vaccine and 5) applicants have not displayed a nexus between the structure of the fragments of SEQ.ID.NO: 1and function of the polypeptide as a vaccine.

As to points 1)- 5), the specification fails to provide a written description of any fragments. The specification fails to teach the critical polypeptide residues involved in the function of the polypeptide SEQ ID NO: 1, such that the skilled artisan is provided no guidance to test, screen or make fragments of the polypeptide or the functionally active fragments of SEQ

ID NO: 1 using conventional technology which allow for a vaccine use in the specification. The specification fails to teach to what extent one could alter SEQ ID NO: 1 and still present the sequence as a vaccine. Even if one were to use the in vivo vaccine methodology of the specification to screen for a vaccine, one of skill in the art would be reduced to merely randomly altering amino acid(s), which would lead to unpredictable results regarding the functional activity of the polypeptide to be used as a vaccine. Moreover, polypeptide chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a polypeptide leads to unpredictable changes in the biological activity of the polypeptide. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the polypeptide (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a polypeptide. Polypeptides with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products

polypeptides that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient to provide for enablement of vaccines. This specification fails to teach any immune response generated by means of a nucleic acid --vaccine. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, 5.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one of the claimed polynucleotide encoding polypeptides or fragments thereof alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. The specification fails to teach that the claimed polynucleotide encoding a polypeptide peptide or fragment or variant thereof are able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize other similar nucleic acids as operative vaccines.

The state of the prior art indicates that little is known about the AMA protein and it's as a vaccine compostion. Hehl et al teaches antiserum to TgAMA1 blocked invasion of host cell only by approximately 40% in *invitro* experiments. However, whether this protein blocks the parasite invasion in animal model is yet to be experimented. At present, the invasion of host cells by asexual stages of apicomplexan parasites is a complex process and receptor-mediated event is still not well understood (Hehl et al, Infection and Immunity, December 2000, p. 7078-

7086, Vol. 68, No. 12). Therefore, the claimed protein induces an effective immune response such that it can block the invasion of parasites completely and it can be used, as a vaccine composition is not predictable in this underdeveloped art. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for any *in vivo* uses of the claimed protein.

In the absence of a teaching of the claimed polypeptide can generate an immune response and that immune response is effective in prevention of disease, the specification is not enabled for vaccines. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

Claim Rejections - 35 U.S.C. 112, second paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 15 is rejected as being vague for the recitation of " functionally active variant." As written, it is impossible to determine the metes and bounds of the term functionally active variant.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 1 is rejected under 35 U.S.C. 102 (b) as being anticipated by Hehl et al 1997, Accession number: AF010264.

The claim is drawn to an isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1.

Hehl et al disclosed an isolated polynucleotide encoding T.gondii apical membrane antigen (AMA1 Tg) comprising the 541amino acid sequence (see the attached accession number). The disclosed protein is 100% identical with the claimed protein, SEQ.ID.NO: 1 Therefore, the prior art anticipated the claimed invention.

15. Claim 1 is rejected under 35 U.S.C. 102 (b) as being anticipated by Hehl et al Accession number: O15681, 1998.

The claim has been discussed supra.

Accession number: O 15681, 1998, disclosed the apical membrane antigen comprising 541 amino acids. The disclosed protein is 100% identical with the claimed protein, SEQ.ID.NO: 1. Therefore, the prior art anticipated the claimed invention.

16. Claims 1-2 and 23-26 are rejected under 35 U.S.C. 102 (a) as being anticipated by Hehl et al 2000, Infection and Immunity, December 2000, p. 7078-7086, Vol. 68, No. 12.

The claims are drawn to an isolated polypeptide comprising an antigenic fragment of SEQ.ID.NO: 1, fusion protein comprising said polypeptide, claims 23-26 are also drawn to TgAMA1binding polypeptide that selectively binds to the isolated polypeptide TgAMA1, wherein said TgAMA1 binding polypeptide is an antibody or antigen binding fragment that specifically binds to a region comprising about 12 or more cysteine residues of the isolated TgAMA1 polypeptide and said binding polypeptide blocks entry of T.gondii parasite into cell.

Hehl et al 2000 disclosed the apical membrane antigen comprising 541 amino acids of SEQ.ID.NO: 1 and fusion proteins comprising said antigen, MBP-LF, MBP – SF and MBP CF (see Page 7079, left column, Materials and Methods through right column up to Generation of fusion proteins and figures 2 and 4). The prior art also discloses TgAMA1 binding polypeptide i.e., polyclonal sera raised against MBP fusion proteins using western-blot analysis (page 7079, right column 4 and 5 th paragraphs and figures 3 and 4). Antibodies to MBP-LF have been shown to bind to secreted sTgAMA1 (figure 7) read on TgAMA1binding polypeptide that selectively binds to the isolated polypeptide TgAMA1. Binding of Monoclonal antibodies, CL22 to AMA protein has been also shown in figure 6. Polyclonal as well as monoclonal antibodies specifically binds to antigen binding fragment because antibodies bind to an antigen binding region or site (antigen binding fragment) of the TgAMA1. Binding to TgAMA1 that comprises about 12 or more cysteine residues is an inherent property because the TgAMA1 protein comprises conserved cysteine residues within the protein's extracellular domain. The prior art disclosed the mouse antisera to recombinant TgAMA1 blocked the invasion of *T.gondii* in host cells (see abstract and figure 8). Hence polyclonal and monoclonal antibodies read on the claims 23-26. Thus the teachings of Hehl et al anticipated the claimed invention.

17. Claims 1 and 23-25 are rejected under 35 U.S.C. 102 (a) as being anticipated by Donahue et al 2000, Molecular Parasitology Meeting, Woods Hole, MA poster Sep, 17 – 21.

The claims are drawn to TgAMA1 binding polypeptide that selectively binds to the isolated polypeptide TgAMA1, wherein said TgAMA1binding polypeptide is an antibody or antigen binding fragment that specifically binds to a region comprising about 12 or more cysteine residues of the isolated TgAMA1 polypeptide.

The prior art also discloses TgAMA1 binding polypeptide i.e., monoclonal antibodies against a 63 kD surface /apical antigen of *T.gondii* tachyzoites which are identified as TgAMA1.

In the absence of evidence to the contrary the TgAMA1 polypeptide inherently comprises the amino acids of SEQ.ID.NO: 1. It appears that antibodies bind to secreted form of TgAMA1. Monoclonal antibodies specifically bind to antigen binding fragment because antibodies bind to an antigen-binding region or site (antigen binding fragment) of the TgAMA1. Binding to TgAMA1 that comprises about 12 or more cysteine residues is an inherent property because the TgAMA1 protein comprises conserved cysteine residues within the protein's extracellular domain (abstract). Thus the teachings of Donahue et al anticipated the claimed invention.

Status of Claims

18. NO claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.
11/13/03

MARK NAVARRO
PRIMARY EXAMINER